REMARKS

Restriction Requirement under 35 U.S.C. § 121

A restriction requirement was made to pending claims 65-72 (Group 1), drawn to a method for treating a lectin-mediated platelet disorder. Group 1 was further restricted into multiple SEQ ID Numbers from which Applicant must elect:

1) one SEQ ID NO selected from the group disclosed in claim 68, consisting of SEQ ID NO:199-247, and 251-290; and

2) one SEQ ID NO selected from the group disclosed in claim 72, consisting of SEQ ID NO:67-117, 129-196, and 293-388.

In response to this restriction/election requirement Applicant hereby elects Group 1 (claims 65-72) and 1) SEQ ID NO:206 and 2) SEQ ID NO:185. For the reasons discussed below Applicant makes this election with traverse and respectfully requests that the Examiner reconsider.

Restriction of nucleic acid ligands identified by the SELEX process, as described in the present case, to only one sequence is an extremely important issue that Applicant has encountered several times in other pending cases. Resolution of this issue is critical to both the present case as well as in other pending and soon to be submitted nucleic acid ligand based cases where multiple nucleic acid ligand sequences are claimed. A good deal of time and effort by both Applicant and United States Patent and Trademark Office (Office) has been expended to resolve this issue on a general level in order that it would not have to be considered in every application that recites claims to multiple nucleic acid ligand sequences. However, as to date efforts to generalize the findings in other cases have not resulted in a general policy on how to treat these unique compounds. Recently, Applicant was able to successfully traverse a restriction requirement in S/N 09/791,301 which had similar numbers of claimed nucleic acid ligand sequences, it is hoped that a similar outcome will prevail in the current case. In addition, and unlike the results in other cases, it is hoped the discussions in the present case can result in a generalized policy formulated for all cases directed at claiming multiple nucleic acid ligands. The new policy will hopefully more appropriately address the unique considerations associated with these molecules. With this in mind, Applicant notes that the present restriction issue, i.e., one nucleic acid ligand/case, goes beyond any one case and

represents a major concern for the Applicant as well as other like Applicants that utilize nucleic acid ligands.

Restriction is discretionary with the Commissioner and must be carefully administered. MPEP §803. Restriction is proper only when it is shown that a patent claims at least two independent or distinct inventions and that examination without restriction would place a serious burden on the Examiner. MPEP § 803. Traditional restriction practice includes guidelines directed to polynucleotide molecules as defined by their nucleic acid sequence. MPEP §803.04. These guidelines balance the interest of aiding the biotechnology industry while not creating an undue or serious burden on the Office. Id. The Office permits a reasonable number of such nucleotide sequences to be claimed in a single application. Ten sequences has been identified as a reasonable number by the Office. Id.

Nucleic acid ligands, *i.e.*, "aptamers", represent a growing and increasingly important tool in the study and treatment of disease. A number of companies, Archemix, SomaLogic, Nuvelo, Elan, etc., are investing large sums of money in the development of this technology with the belief that their findings can and will be protected under current US patent law. However, as will be discussed more fully below, the present restriction practice, *i.e.*, applying Office rules used to restrict protein encoding nucleic acids (nucleic acid sequences), to these unique nucleic acid ligand members is resulting in an intolerable and cost-prohibitive road-block to the development of novel aptamer based therapeutics. Applicants respectfully submit that it is wholly unreasonable and inappropriate to apply current Office policy regarding examination of nucleic acid sequences to nucleic acid ligands and will show that only a minimal burden is placed on the Examiner to examine nucleic acid ligand sequences as long as all the ligands are to a common target molecule. To continue treating these ligand molecules as equivalent to protein encoding nucleic acid sequences will likely have a chilling effect on continued aptamer research and product development.

As such, Applicants respectfully submit that examination of all 299 claimed sequences in the present application would not put an undue burden on the Examiner, and further that failure to allow such examination represents a significant detriment to the Applicant's business and in a general sense to the entire nucleic acid ligand industry.

On March 12, 1996, the Office invited the public to comment on the problem created by the filing of patent applications claiming large numbers of nucleic acid sequences. See 61 Fed. Reg. 9980. Specifically, the Office noted that "scientific and technological advances have permitted researchers to identify large numbers of gene fragments rapidly." Id. The filing of patent applications claiming those gene fragments, termed Expressed Sequence Tags (ESTs), posed numerous problems for the Office due to the cost associated with the extensive database searches that must be performed during examination.

At a public hearing held on April 16, 1996, then-Commissioner Bruce Lehman noted that at least 70 patent applications comprising 200,000 claimed sequences were currently pending. Commissioner Lehman further pointed out that the number of patent applications was growing, and that "based on the number of organisms in [sic and] genes still to be discovered, such growth will continue for the near future."

In response to the comments received, the USPTO announced a new examination policy as follows:

> Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such [coding] nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141.
>
> 1992 O.G. 68

From the above discussion, it is abundantly clear that the overriding motivation for this policy came from the burden imposed on the USPTO through the filing of patent applications claiming hundreds and thousands of different organismal coding sequences, *i.e.*, patent applications that claim different genes and fragments from different genes (ESTs). Because such sequences encode different proteins, there is no unity of invention.

Applicant's applications (as well as other aptamer industry based applications), including the instant one, have nothing to do with genes or gene products. Nucleic acid ligands are non-coding sequences. Nucleic acid ligands are not isolated from any

organism; they are, by definition, non-naturally occurring molecules. Each nucleic acid ligand is identified by the SELEX process from a synthetic candidate mixture of randomized nucleic acid sequences. The SELEX process selects those nucleic acids in the candidate mixture that have the ability to bind to a particular target, i.e., unity of invention. Nucleic acid ligands are not selected for their ability to encode proteins. In fact, nucleic acid ligands do not even encode proteins, that is any coding potential that a nucleic acid ligand may possess is fortuitous and plays no role whatsoever in the binding of the nucleic acid ligand to its cognate target. It, therefore, seems wholly unreasonable and inappropriate to apply a policy aimed at curbing excessive numbers of different genes and different gene fragments to nucleic acid ligands.

Furthermore, the Office policy is directed towards patent applications that claim multiple coding sequences, each coding for a different protein. Because the sequences code for different proteins, there is clearly no unity of invention. Nucleic acid ligands that bind a single target, in contrast, are unified in their function. This unity of function further distinguishes applications that claim nucleic acid ligands from applications that claim different coding sequences, and further illustrates the inappropriateness of requiring restriction in the former case. In the instant application, the nucleic acid ligands bind to either P-selectin (SEQ ID NO:199-247, and 251-290) or L-selectin (SEQ ID NO: 67-117, 129-196, and 293-388). Applicants submit that restriction to either nucleic acid ligands that bind P-selectin or to nucleic acid ligands that bind to L-selectin is appropriate, but that further restriction is not.

Applicant also contends that it is inappropriate to apply current restriction policy to nucleic acid ligands because for coding sequences, similarity must be determined both at the overt nucleotide level, and also at the amino acid level of the encoded protein. Each amino acid can be coded for by 1-6 different codons, so it is possible for identical proteins to be coded for by nucleotide sequences that bear as little as 70% identity to one another. For example, in the case of *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993), the Court heard that the number of sequences that could potentially encode human IGF-1 would exceed 1036 due to this degeneracy of the genetic code. This creates additional search problems since gene patents frequently claim the disclosed sequences very broadly as explained below:

For example, typical claims include the sequence and any sequence having a certain percentage identity or homology to the sequence or any sequence which hybridizes to the sequence, with or without the conditions of binding being recited. Others recite the sequence or any fragment of the sequence having a particular length of nucleotides. These claims are largely responsible for the lengthy search and evaluation times and the high resultant costs to the PTO.

61 Fed. Reg. at 9980 (emphasis added).

In contrast, searches for nucleic acid ligands are far simpler than those for coding sequences. Since nucleic acid ligands do not code for proteins, and since more limited sequences are claimed, the searches can be performed in a vastly shorter time and at greatly reduced cost in comparison with gene patent searches. The differences in the complexity of the searches once again illustrates the inappropriateness of adhering to the one sequence (reasonable number)/patent guideline for nucleic acid ligands and clearly demonstrates that there is no serious burden on the Examiner. In contrast, and mentioned above, the burden on Applicant and others within the aptamer industry to protect one nucleic acid ligand/patent is immense, requiring that every restriction requirement be fought through appeal in hopes of maximizing the coverage within each potential patent.

Importantly, Applicants respectfully point out that searching for nucleic acid sequences that exactly match those of the claimed nucleic acid ligands is, moreover, an unnecessary endeavor. Since nucleic acid ligands are non-naturally occurring and are derived from randomized sequence, the likelihood of finding the same sequence in any genomic database is small.

Because nucleic acid ligands do not occur in animal genomes, the only prior art sources that need be searched are those references and databases that list nucleic acid ligands to the same target as the subject application. This is a much smaller number of prior art sources in comparison to the number of sources that must be searched when a patent claims coding sequences and polymorphisms. Moreover, Applicants would also point out that even if there is a prior art description of nucleic acid ligands to the same targets as in the instant application, the likelihood that the prior art ligands will have the

same sequence as the instant nucleic acid ligands is vanishingly small. In other words, if the SELEX process were to isolate a high affinity sequence to some target protein, it is highly unlikely that a second in vitro selection, starting from an independent candidate mixture, would isolate the same exact sequence. This will be demonstrated in the following paragraphs.

SELEX process candidate mixtures (also referred to as "libraries") are comprised of sequences with N nucleotides in the random region. Since there are 4 possible nucleotides at each position, there exist 4^N unique sequences in the N-random library. In the case where N = 30, for example, this means that there are $4^{30} = 1.15x10^{18}$ unique sequences. Typically, the SELEX process starts with an initial random library of 10^{14} individual sequences. We wish, then, to compute the probability that two independent libraries of 10^{14} sequences will contain at least one copy of the identical winning sequence given a total library complexity of 4^{30}.

Given a sequence of interest, it is easier to compute the probability that none of the 10^{14} sequences in the starting library correspond to the sequence of interest. The probability that the first sequence is not the one of interest is simply:

$$P = (1-1/4^N) \qquad (1)$$

The probability that none of the 10^{14} sequences is the sequence of interest is the joint probability that each sequence differs from the target one. This probability is the product of equation (1) over all the 10^{14} sequences in the starting pool:

$$P = (1-1/4^N)(1-1/4^N)...(1-1/4^N) = (1-1/4^N)^{10^{14}} \qquad (2)$$

The probability that a pool will have at least one copy of the sequence of interest is then:

$$P = 1 - (1 - 1/4^N)^{10^{14}} \quad (3)$$

Equation 3 is exact; however, it is untractable for computing probabilities here since the numbers are so large. A good numerical approximation to the probability in equation (2) may be derived when one realizes that the probability associated with a particular sequence is small, 4-N. Therefore, we can neglect all the cross products of equation (2), giving, to a first approximation:

$$P \sim 1 - 10^{14}/4^N \quad (4)$$

The approximate probability of finding the sequence of interest at least once in the starting pool is then:

$$P \sim 10^{14}/4^N \quad (5)$$

In a typical nucleic acid ligand scenario where N = 30, the probability of finding the sequence of interest at least once in the starting pool according to equation (5) is $p = 8.7 \times 10^{-5}$. In other words, if one knows the sequence of a particular nucleic acid ligand of a target, one would need to perform more than eleven thousand SELEX experiments against the same target in order to even find one copy of that same sequence in the initial candidate mixture. The probability of actually selecting that single copy of the sequence again as one of the "winning" nucleic acid ligands of the target after multiple rounds of the SELEX process is likely to be even more remote. This is because it is easy to lose a given nucleic acid, even one that binds tightly to a target, from the first round of the SELEX process when it is present only as a single copy. Hence, Applicants assert that even searching a database restricted to nucleic acid ligands to the same target (which in itself would be a far more restricted, and hence simpler, search than those for ESTs and polymorphisms) would also be an unnecessary endeavor because the likelihood that the same nucleic acid ligand has been described before is extremely remote. This is exactly

the conclusion Examiner Zitomer came to in the S/N 791,301 case, where the Examiner commented: "applicant was advised that on reconsideration examiner had determined that no nucleic acid ligand sequences would be searched in view of the findings in the Patent Office and in the office of applicant's representative that nucleic acid sequences are not found among the coding sequences in the public databases." (Exhibit A)

Applicant would further note that even if the particular nucleic acid ligand sequence (structure) was identified in a given search, an Examiner would still need to show that the identified sequence had the same claimed function (as in the case of the pending claims) for it to be effective art. This is particularly relevant as the present claims are directed toward a method for treating a lectin-mediated disorder or inflammation and not toward an nucleic acid ligand composition. As such, the Examiner would search the limitations of the particular method claim without reliance on any particular ligand sequence. Only when a search of the method claim resulted in a hit would the Examiner be required to search the particular ligand sequence at issue. These arguments again illustrates that an Examiner has numerous means to fairly and effectively examine claims that include nucleic acid ligands without limiting them to a small number of sequences.

Applicants assert that no serious burden would be imposed by examination of the claims as filed. Applicants have demonstrated that, unlike genes and gene fragments, multiple nucleic acid ligands can be examined without serious burden in a single application. Specifically, Applicants have shown that it is unnecessary to search for a particular nucleic acid ligand in any prior art database as the chance of finding the identical sequence in the prior art is remote. Further, the burden imposed by these restriction requirements on Applicant and Applicant's industry is extreme, limiting the potential of this extremely important therapeutic industry.

Finally, Applicant notes that the proposals herein are aligned with the Proposed Rule Changes to Focus The Patent Process in the 21st Century. The proposals herein show that examination of nucleic acid ligands to a target molecule can be, and should be, performed in a single case. This consolidation into one case is efficient, promotes innovation by encouraging companies to pursue nucleic acid ligands (otherwise the cost is unacceptably high to file on each sequence given the above discussion) and provides

high quality patent protection. For all the reasons above Applicant respectfully request reconsideration of the restriction requirement in the present case. For all these reasons, Applicants respectfully submit that the restriction requirement is in error and request reconsideration thereof.

Should the Examiner maintain the restriction requirement, Applicants pursuant to 37 C.F.R. § 1.143 request the right to file a divisional application at a later time, or to the Applicants' right to petition the Commissioner for reconsideration of the restriction requirement pursuant to 37 C.F.R. § 1.144.

If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned. The Undersigned would also make himself available to visit the Office to discuss these issues in person and would encourage such a meeting where Applicant, Examiner and Examiner's supervisor are present.

This Response is filed with a petition and corresponding fee for extension of time extending the time for response to October 18, 2006. This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: 10/17/06

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EXHIBIT A

Interview Summary	Application No. 09/791,301	Applicant(s) PAGRATIS et al.
	Examiner S. Zitomer	Art Unit 1634

All participants (applicant, applicant's representative, PTO personnel):

(1) *S. Zitomer, Examiner* (3) _____

(2) *Barry Swanson For Applicant* (4) _____

Date of Interview *Aug 30, 2002*

Type: e)☒ Telephonic b)☐ Video Conference
c)☐ Personal (copy is given to 1)☐ applicant 2)☐ applicant's representative)

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No. If yes, brief description:
Copy of amendment and response to Restriction Requirement for election of a single nucleotide sequence was faxed to the examiner on August 26, 2002.

Claim(s) discussed: *N/A*

Identification of prior art discussed:
N/A

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Discussed were applicant's arguments set forth in the response to USPTO requirement for restriction of examination to single or up to 10 nucleotide sequence inventions. The arguments are based on the close sequence similarity of nucleic acid ligands to a particular target and on the futility of searching extent coding sequence databases in view of applicant's experience of absence of significant hits in hundreds of searches. The latter was corroborated by examiner from past searches of hundreds of nucleic acid ligand sequences by STIC prior to current restriction practice. Pursuant to discussion with SPE Gary Jones, examiner determined to exercise examiner discretion in restriction practice and require 5 nucleic acid ligand sequences to be selected by applicant in all present and future nucleic acid ligand applications in which claims contain nucleotide sequences. The selected sequences will be searched by STIC to demonstrate for the record the absence of hits on prior art non-nucleic acid ligand sequences.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☒ It is not necessary for applicant to provide a separate record of the substance of the interview (if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached

STEPHANIE W. ZITOMER
PRIMARY EXAMINER

Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.